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REVIEW

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Antifungal stewardship considerations for adults and pediatrics

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ABSTRACT

Antifungal stewardship refers to coordinated interventions to monitor and direct the appropriate use of antifungal agents in order to achieve the best clinical outcomes and minimize selective pressure and adverse events. Antifungal utilization has steadily risen over time in concert with the increase in number of immunocompromised adults and children at risk for invasive fungal infections (IFI). Challenges in diagnosing IFI often lead to delays in treatment and poorer outcomes. There are also emerging data linking prior antifungal exposure and suboptimal dosing to the emergence of antifungal resistance, particularly for *Candida*. Antimicrobial stewardship programs can take a multi-pronged bundle approach to ensure suitable prescribing of antifungals via post-prescription review and feedback and/or prior authorization. Institutional guidelines can also be developed to guide diagnostic testing in at-risk populations; appropriate choice, dose, and duration of antifungal agent; therapeutic drug monitoring; and opportunities for de-escalation and intravenous-to-oral conversion.

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Introduction

Antifungal stewardship refers to coordinated interventions to monitor and direct the appropriate use of antifungal agents in order to achieve the best clinical outcomes and minimize selective pressure and adverse events.[1] The principles of antifungal stewardship parallel those of established antimicrobial stewardship programs (ASPs) whereby antifungal prescribing is optimized by taking into account the spectrum of activity, pharmacokinetic and pharmacodynamic (PK-PD) properties, duration, and route of administration.[2] Antifungal stewardship may already be employed by existing ASPs due to the high cost of these drugs, the potential for toxicity with prolonged use, and the need for expertise to guide clinicians in prescribing.[1] While not a primary consideration, reduction in healthcare costs is frequently a secondary stewardship effect.[3] Due to growing public awareness of the perils of resistant bacteria, many ASPs have focused initial efforts on reducing inappropriate antibiotic use. However, the increasing numbers of immunosuppressed patients at risk for opportunistic infections entail attention to other anti-infective classes.[4-6] We aim to discuss why antifungal stewardship is needed; how to implement antifungal stewardship with a reflection on rapid diagnostics, management of drug-drug interactions, and therapeutic drug monitoring (TDM); what metrics to consider; and whether published studies to date of ASPs employing antifungal stewardship interventions have demonstrated improved antifungal utilization without adversely affecting patient outcomes.

The case for antifungal stewardship

The health and economic impact of invasive fungal infections

Antifungal consumption is intimately linked to the burden of fungal disease. Invasive fungal infections (IFI) have increased in frequency over the last 2 decades. This is due in part to the growing number of persons at risk for the development of IFI, including patients with medication-induced immunosuppression, those undergoing major surgery (especially involving the bowel), and patients at the extremes of age.[7] Patients undergoing treatment for a hematologic malignancy or recipients of haematopoietic cell (HCT) or solid organ (SOT) transplantation are particularly vulnerable. Thus, the epidemiology of IFI in these specific patient groups will be highlighted here.

Although patients with hematologic malignancies comprise an important group susceptible to IFI development, they are not at equal risk. In a large multicenter,

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retrospective cohort study, Pagano and colleagues found that the overall incidence of IFI was 4.6% among patients 16 y and older with hematologic malignancies, but there was variability across the different patient subsets.[8] Individuals with acute myeloid leukemia (AML) (12%) had the highest rate, followed by those with acute lymphoid leukemia (6.5%), chronic myeloid leukemia (2.5%), chronic lymphoid leukemia (0.5%), lymphoma (0.7%–1.6%), and multiple myeloma (0.5%). This same study found that invasive aspergillosis (IA) (310 of 538 cases) and invasive candidiasis (IC) (175 of 538 cases) were the predominant infections and that the IFI-attributable mortality according to infecting species was 33% for IC, 42% for IA, and 64% for mucormycosis.

The epidemiology of IFI in transplant patients has recently been updated for the United States (US). The Transplant-Associated Infection Surveillance Network (TRANSNET), a consortium of 23 US transplant centers, prospectively identified HCT recipients with proven or probable IFI between March 2001 and March 2006 and found an overall 12-month IFI cumulative incidence (CI) of 3.4%, although there was variability across institutions (0.9%–13.2%) and type of transplant (autologous HCT, 1.2%; allogeneic HCT with matched-related donor, 5.8%; allogeneic HCT with unrelated donor, 7.7%; allogeneic HCT with mismatched-related donor, 8.1%).[9] This same report noted that IA (43%) was the most common IFI occurring in HCT recipients, followed by IC (28%) and mucormycosis (8%). This finding differed from previous decades when IC was the predominant IFI and may be due to the widespread use of azole prophylaxis although other factors may also be playing a role.[10] Overall 1-year survival among the HCT cohort with IA, IC, and mucormycosis was 25.4%, 33.6%, and 28%, respectively.[9]

Using similar methodology, 15 transplant centers in the TRANSNET contributed prospective surveillance data for SOT patients from March 2001 to March 2006 and calculated the overall 12-month IFI CI to be 3.1% with variability by site (1.2%–6.1%) and the type of organ being transplanted (small bowel, 11.6%; lung and heart-lung, 8.6%; liver, 4.7%; pancreas and kidney-pancreas, 4%; heart, 3.4%; kidney, 1.3%).[11] There were some differences with the TRANSNET HCT cohort. IC (53%) accounted for the bulk of IFI occurring in SOT, followed by IA (19%) and cryptococcosis (8%). In addition, the 12-month survival after infection with IC (66%) and IA (59%) was higher in comparison to HCT recipients.

In addition to the significant morbidity and mortality associated with IFI, the economic impact of IFIs is considerable. In one case-control study of patients with acute leukemia or HCT recipients, having an IFI was associated with an excess median attributable hospital cost (inclusive of antifungal treatment and ward cost) of US$21,203, increasing to US$54,993 with intensive care unit (ICU) requirement.[12] Another case-control study found that case-patients receiving adequate treatment for IC had increased length-of-stay (LOS) by 3 to 13 days, as well as $3,000 to $22,000 more in hospital costs compared to controls.[13] This same study found that patients were more likely to die when inadequate candidemia treatment was administered.

Delays in diagnosis and appropriate therapy for IFI are associated with poorer outcomes across a broad array of fungi, including *Candida, Aspergillus*, mucormycosis, and *Pneumocystis jiroveci*.[14-18] The difficulty in establishing an early diagnosis is related to the nonspecific clinical features and the low sensitivity of microscopy, histologic examination, conventional radiology, and cultures.[19] Recognizing the difficulties in diagnosis plus the awareness of harm associated with delays in appropriate treatment has prompted many clinicians to choose to empirically start antifungal treatment. There is also keen interest in prophylactic strategies to prevent IFI in high-risk patients. The question is whether these practices are leading to overuse or inappropriate antifungal use.

Antifungal utilization in adults and pediatrics

While sales numbers with the introduction of new antifungal agents have increased, there are few reliable and systematically reported data on antifungal consumption in adults. Several studies have found that fluconazole is still the most frequently prescribed antifungal agent despite the market introduction of echinocandins and mold-active azoles.[20-23] In terms of available benchmarking data, one study examined antifungal utilization between 2001–2003 and 2008–2011 at 5 academic teaching hospitals in Germany.[20] These hospitals were tertiary care referral centers with all major services including HCT, SOT, and level one trauma capabilities. Drug use densities were calculated as yearly recommended daily doses (RDD) per 100 patient-days. Despite variabilities in prescribing patterns among the hospitals, there was increased utilization of systemic antifungal drugs in both study periods, and the main consumers were the surgical and medical ICUs as well as the hematology-oncology services. In another study, Meyer et al. found that antifungal utilization was heterogenous in 13 ICUs across Germany between January 2004 through June 2005 and that ICUs treating transplant patients (153 defined daily dose (DDD)/1000 patient-days) had higher consumption compared to ICUs not treating transplant patients (46 DDD/1000 patient-days).[21]

The data on antifungal utilization in pediatrics are sparse but show similar trends. A single-center study at a Canadian university hospital (400 pediatric beds and 100

obstetrics-gynecology beds) found a 2.97-fold increase in the overall number of DDD per 1000 patient-days, from 14.8 in 2000–2001 to 37.5 in 2005–2006 and 43.9 in 2010–2011.[24] When the investigators switched to the preferred metric for pediatrics, the findings continued to show a 2.97-fold increase in the overall number of days of therapy (DOT) per 1000 patient-days, from 22.8 in 2000–2001 to 50.3 in 2005–2006 and 67.8 in 2010–2011. The upsurge in antifungal consumption was attributed to the increased numbers of hematology-oncology, transplant, and neonatology patients being seen and the accompanying expansion of antifungal prophylaxis and treatment for these patient groups.

The pediatric literature also brings to light other interesting issues. For one, there appears to be significant variability in prescribing practices across institutions and geographic regions for prophylaxis and treatment of IFI despite the availability of consensus guidelines.[25-27] Another challenge is achieving appropriate dosing. A point-prevalence study of antimicrobial use in hospitalized neonates and children from 226 centers around the world found that only 371 (42%) of 885 evaluable patients received a total daily dose of an antifungal drug within the dosing range recommended in current guidelines, and subtherapeutic doses were prescribed in 416 (47%) cases.[28] While dosing varied across countries and regions, no specific relationship was found between geographical distribution and the proportion of patients receiving subtherapeutic dosing. Part of the problem stems from the inadequacy of PK-PD data for neonates and children.[29] There is also lack of evidence-based recommendations for what constitutes optimal dosing in pediatric patients, particularly for the older, more commonly prescribed drugs like fluconazole and amphotericin B deoxycholate.[28] Well-designed clinical studies in conjunction with PK modeling and simulation to guide antifungal stewardship efforts in pediatrics are urgently needed.

While the aforementioned adult and pediatric studies have shown increased antifungal utilization over time, none assessed for prescribing quality, so it is difficult to know what proportion would have been deemed unnecessary use. Nevertheless, gathering baseline pharmacoepidemiological data is important for observing prescribing trends and identifying areas for improvement. Such data may also be useful in studies correlating drug utilization to antifungal resistance.

Emerging antifungal resistance

Although *Candida* and *Aspergillus* species have had predictable antifungal susceptibility results in the past, antifungal resistance is emerging. In 2013, the Centers for Disease Control and Prevention (CDC) published a landmark report on antimicrobial resistance that listed fluconazole-resistant *Candida* species among the pathogens posing a serious threat to human health.[30] However, the increased therapeutic use of echinocandins for IC may be affecting resistance patterns. Cleveland et al. noted a shifting epidemiology of *Candida* resistance in 2 major US metropolitan areas between 2008 and 2013 via population-based laboratory surveillance.[31] While they documented a drop in fluconazole resistance, there was also a small but perturbing increase in isolates resistant to echinocandins and the emergence of multidrug-resistant *Candida*, almost all of which were due to *C. glabrata*. Not surprisingly, substantially higher resistance rates have been reported in oncology patients. At one cancer treatment center, 30 (20.5%) of 146 *C. glabrata* blood culture isolates between March 2005 and September 2013 were resistant to fluconazole, 15 (10.3%) to caspofungin, and 10 (6.8%) to multiple drugs.[32] Furthermore, the incidence density of candidemia due to uncommon species increased significantly from 1.89 episodes per 100,000 inpatient days (1998–2005) to 4.2 episodes per 100,000 inpatient days (2006–2013, $P = 0.0001$) and was associated with the continuous increase in echinocandin use at the same institution.[33] These evolving resistance patterns emphasize the importance of understanding the local and regional epidemiology; however, few hospitals report fungal susceptibilities in their antibiograms.[34, 35]

Correlating antifungal usage with the emergence of antifungal resistance in *Candida* is beginning to be established. A French multicenter surveillance program evaluated 2,538 candidemia episodes among adults and children over a 7-year period.[36] Exposure to fluconazole or caspofungin within 30 d prior to candidemia was related to a decreased prevalence of *C. albicans* in favor of non-albicans *Candida* species ($P = 0.001$). In addition, previous receipt of fluconazole or caspofungin was associated with an increased risk of infection due to an isolate with reduced susceptibility to fluconazole (OR 2.17, 95% CI 1.51–3.13, $P < 0.001$) or caspofungin (OR 4.79, 95% CI 2.47–9.28, $P < 0.001$), respectively. Other reports are finding similar associations between antifungal utilization and changes to the distribution and drug susceptibilities of *Candida* species.[37,38] Appropriate dosing also matters since Shah and colleagues found that suboptimal initial dosing of prior fluconazole therapy was linked to subsequent candidemia due to fluconazole-non-susceptible *Candida* species.[39]

Antifungal resistance among *Aspergillus* species is a concerning issue as well. A multicenter surveillance study of 3,788 *Aspergillus* isolates in 22 centers from 19 countries documented a 3.2% prevalence of azole-resistant

A. fumigatus; azole resistance was detected in 11 of 17 European centers from 9 countries with TR_{34}/L98H being the predominant mechanism of resistance.[40] The investigators also noted that among the patients with resistant isolates, 28 had documented IA with a 70% case-fatality rate. There are some data to suggest that exposure to agricultural azoles may lead to cross-resistance with azoles used in medical practice.[41,42] In the Netherlands where widespread azole resistance has been found, the dominance of the TR_{34}/L98H mechanism and the high proportion of resistant isolates recovered from azole-naïve patients lend support to this thinking.[43] Because resistance rates can differ among the hospitals and microbiologic recovery of *Aspergillus* also may vary among different patient populations, determining epidemiology at the hospital level and among patient subgroups by infection control is essential to enable ASPs to modify institutional guidelines for prophylaxis and treatment of IA accordingly.[44] In addition, this emerging problem highlights the importance of following standardized infection control practices to reduce the risk of nosocomial aspergillosis in high-risk patients and the urgent need to develop tests to rapidly identify azole-resistant *Aspergillus* species.[45]

Implementation of antifungal stewardship

The increase in antifungal consumption and the reports relating antifungal utilization to the development of antifungal resistance necessitate optimization of antifungal drugs at centers caring for patients at risk for IFI. There is an emerging literature about how to conduct antifungal stewardship. The nuts and bolts for how to develop an ASP have been well described in the 2007 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guideline.[3] In the updated 2016 IDSA and SHEA guideline, prior authorization and/or post-prescription review and feedback are recommended over no such interventions and can be enhanced with supplemental strategies including but not limited to formulary restriction, guideline development, prescriber education, antimicrobial de-escalation, and intravenous (IV)-to-oral conversion.[2] ASPs can adapt these programmatic elements to improve prescribing of antifungal and other anti-infective drug classes, not just that of anti-bacterial agents.[2]

If there are patient populations at risk for IFI, ASPs may also be working with clinical microbiology to consider incorporating rapid diagnostics and azole level monitoring for the diagnosis and management of IC and IA at their respective institutions. Although invasive mucormycosis should be considered in the differential diagnosis for patients with suspected IFI, diagnosis still relies on histopathologic and culture confirmation; studies looking into the feasibility of using polymerase chain reaction (PCR) on tissue specimens and serum remain investigational to date.[46]

Improving diagnosis of invasive candidiasis

Candidemia is the fourth most common nosocomial bloodstream infection in the US.[47] While the gold standard is blood culture, the overall sensitivity has been reported to be 50%.[48] In addition, the median time-to-positivity is 2 to 3 days, and species identification can take an additional one to 2 d. Starting empiric antifungal therapy >12 hours after the time of drawing the first positive blood culture is associated with greater hospital mortality.[14] The need for swift results is evident, and there are several rapid molecular identification methods that can provide results within minutes to a few hours. These include matrix-assisted laser desorption/ ionization time-of-flight (MALDI-TOF) spectrometry, multiplex PCR, and peptide nucleic acid fluorescent *in situ* hybridization (PNA FISH).[19,49] Test characteristics for all 3 are described in Table 1.

While MALDI-TOF or multiplex PCR combined with antimicrobial stewardship (AS) intervention appears promising in the management of patients with bacterial bloodstream infections, published studies to date had few candidemia episodes to draw definitive conclusions.[50,51] Regarding PNA FISH, Forrest and colleagues utilized a *C. albicans*-specific probe for yeast-positive blood cultures in 2004; all PNA FISH results were reported to the ASP since approval was required to release antifungal therapy to the primary teams.[52] The median time required to identify *C. albicans* compared to conventional culture (9.5 hours vs 44 hours, $P < 0.001$) was significantly reduced. In addition, there was considerable reduction of caspofungin usage in patients with candidemia due to *C. albicans* compared to the previous year when PNA FISH was not used (2004: 3.2 DDD/patient vs 2003: 8.7 DDD/patient, $P < 0.05$), resulting in an overall cost savings of $1,729 per patient. Another study implemented the Yeast Traffic Light PNA FISH (AdvanDx, Woburn, MA) that differentiates among 5 *Candida* species along with AS intervention and found reduced median time to organism identification (0.2 d vs 4 days, $P < 0.001$) and improved mean time to appropriate therapy (0.6 d vs 2.3 days, $P = 0.0016$) when compared to conventional methods.[53] There was no difference in hospital LOS or mortality.

There has also been the development of non-culture-based diagnostics, including PCR and (1–3)-β-D-glucan assay (BDG), to try to identify deep-seated infections that may be missed by blood culture alone. A discussion of each test and its specifications is beyond the scope of

Table 1. Comparison of rapid identification methods for *Candida*.

	Matrix-assisted laser desorption/ ionization time-of-flight	Multiplex polymerase chain reaction	Peptide nucleic acid fluorescent *in situ* hybridization	T2 Magnetic Resonance
Abbreviation	MALDI-TOF	Multiplex PCR	PNA FISH	T2MR
Blood culture-based?	Yes	Yes	Yes	No
Identification	>200 clinically relevant bacteria and yeast species	24 bacteria and yeast (including 5 species of *Candida*) and 3 antibiotic resistance genes	Up to 5 species *Candida*	5 species of *Candida*
Hands-on time	1 minute	2 minutes	5 minutes	<5 minutes
Turnaround time	5 minutes	60 minutes	90 minutes	180 to 300 minutes
United States Food and Drug Administration-approved?	Yes	Yes	Yes	Yes
Trade name	VITEK MS (bioMerieux) MALDI Biotyper CA (Bruker Corporation)	FilmArray Blood Culture Identification (BioFire Diagnostics)	*C. albicans/C. glabrata* PNA FISH (AdvanDx) Yeast Traffic Light (AdvanDx) (5 species of *Candida*: *C. albicans, C. parapsilosis, C. tropicalis, C. glabrata, C. krusei*)	T2 Candida Panel (T2 Biosystems)
Studies using stewardship intervention	Yes	Yes	Yes	No

this paper but has already been extensively reviewed.[19,48] In a recent study, Nguyen et al. compared the performance of a validated *Candida* real-time PCR and BDG to blood culture in 55 patients with IC and found that both tests were more sensitive than blood cultures among patients with deep-seated infection, signifying their usefulness as diagnostic adjuncts (88% and 62% vs 17%; $P = 0.0005$ and $P = 0.003$).[54] Another promising assay is the T2Candida Panel (T2 Biosystems), a US Food and Drug Administration (FDA)-cleared test to detect 5 species of *Candida* directly from whole blood without need for culture or nucleic acid extraction within 3 to 5 hours (Table 1).[55] In their appraisal of clinical studies to date, Pfaller and colleagues noted that the T2Candida Panel also detected all 12 confirmed cases of deep-seated infections in patients with negative blood cultures, suggesting a potential role to diagnose previously unrecognized *Candida* infections.[56] Additional studies are certainly warranted to see if PCR, BDG, or T2Candida Panel can improve antifungal utilization and patient outcomes for IC, but their benefits may not be fully realized if there is absence of real-time AS intervention.[57]

Improving diagnosis of invasive aspergillosis

Although *Aspergillus* species are ubiquitous in nature and inhalation of infectious conidia is a common event, tissue invasion is uncommon unless the patient is immunocompromised. Classic risk factors include prolonged neutropenia, receipt of high-dose steroids, and impaired cellular immunity.[58] Diagnosis of IA is based on a scale of certainty, ranging from proven to probable to possible.[59] Direct visualization of branching septate hyphae in tissue or recovery of *Aspergillus* from a sterile site provides definitive evidence. However, biopsy is not always feasible due to concern for complications (e.g., bleeding risk in patient with thrombocytopenia). Attention has thus turned to the application of non-culture-based methods, and previous reviews have detailed the test performance and caveats of using BDG, galactomannan (GM) antigen detection, and PCR.[19,60] In general, results of non-culture-based tests should be interpreted in conjunction with other clinical, radiographic, and microbiologic criteria for IA.[61,62]

With respect to serum BDG and GM assays, several meta-analyses have noted heterogeneity of results attributed to differences in study design, patient populations (e.g., hematologic vs other), the criteria used to define a positive test, and the definition of IA.[63-68] Among high-risk patients with hematologic malignancies and chemotherapy-induced neutropenia or allogeneic HCT, both tests share a similar sensitivity of 60%–80% and specificity of 90% and higher.[69] There may also be a role for combining serum BDG and GM screening in high-risk neutropenic patients. In a retrospective analysis, Pazos and colleagues found similar kinetics for BDG and GM (although BDG tended to turn positive earlier than GM) and suggested that concomitant detection of both markers likely aids diagnosis of IA whereas discordant findings may be indicative of false-positive results.[70] Detection of BDG and GM was also observed to occur several days prior to the onset of fever, computed tomography (CT) abnormalities, and the initiation of antifungal therapy in most cases of proven or probable IA, suggesting that appropriate screening could shorten the time interval between suspected infection and established diagnosis.[70] However, larger, prospective evaluations are needed to confirm these findings. Data for use of BDG and GM in SOT are not as well supported and could be

explained by the limited angio-invasion in patients with better immune defenses compared to neutropenic patients.[63]

The overall sensitivity and specificity of bronchoalveolar lavage (BAL) GM has been reported to be 85% and 90%–95%, respectively.[71,72] While data for BAL GM suggest that a higher optical density (OD) cut-off (1.0 vs 0.5) increases specificity, the FDA considers an OD index of at least 0.5 to be positive.[72] In contrast to the serum assay, BAL GM seems to perform well in SOT recipients.[73,74] There are no data to support the use of BDG testing in BAL.[69]

Multiple causes of false-positive results for both BDG and GM have been reported, such as concomitant bacterial infections, β-lactam antibiotics, blood transfusions, blood-derived products, gluconate sodium-containing products, renal replacement therapy, and cross-reactivity with other fungi.[62] For GM, concurrent administration of piperacillin-tazobactam was a concern, but newer formulations of the drug seem to have lowered the risk for false-positive results.[75,76] False-negative results have been linked to the pathogenesis of IA with varying degrees of angio-invasion and dissemination according to the level of host immunosuppression.[69]

When used as screening tests for IA in high-risk groups, PCR has demonstrated moderate diagnostic accuracy with sensitivity and specificity ranging between 81%–84% and 76%–79%, respectively.[61,77] In addition, serial positive PCR results are highly indicative of IA,[61,77] and the combination of PCR and BAL GM has been suggested for improved sensitivity without loss of specificity.[78] However, clinical studies are limited by the lack of methodologic standardization and multicenter validation; there are no commercially approved PCR assays to date.[78]

One area of interest is whether non-culture-based tests can shift the emphasis away from empiric to preemptive antifungal therapy. Maertens et al. conducted a feasibility study in which neutropenic patients undergoing myeloablative allogeneic HCT or chemotherapy for acute leukemia or myelodysplastic syndrome (MDS) received fluconazole prophylaxis and were screened daily for the presence of GM via enzyme immunoassay (EIA).[79] A diagnostic evaluation consisting of high-resolution CT of the chest (plus/minus sinus) and bronchoscopy with lavage was performed on the basis of defined clinical, radiographic, and microbiologic criteria. Antifungal therapy was only initiated in patients with 2 or more consecutive GM EIA assays with an index of $\geq$0.5 or with CT findings suggestive of IFI that were supported by microbiologic data. This diagnosis-driven strategy reduced the rate of antifungal use from 35% to 7.7%, and there were no undetected cases of IA. Since then, there have been several randomized, controlled trials comparing empiric to the preemptive approach, but heterogeneity in study designs makes interpretation of the results challenging (Table 2).[80-82] As such, the safety and efficacy of replacing empiric with preemptive antifungal therapy in neutropenic patients have not been established; additional prospective studies are needed. Also, the finding that posaconazole causes the serum GM surveillance of asymptomatic patients to be unreliable brings the relevancy of the preemptive strategy into question at those centers that routinely employ effective anti-mold prophylaxis.[83]

Interestingly, Stanzani and colleagues have proposed a radiology-driven diagnostic algorithm as an alternative to non-culture-based biomarkers since the "occluded vessel" sign seen on CT pulmonary angiography (CTPA) in patients with hematologic malignancies and proven or probable IA appears to have similar diagnostic performance (sensitivity 83%, specificity 93%) to serum GM.[84] Patients at their institution first undergo individualized risk assessment using a weighted risk prediction score to discriminate between those at low (<1 % incidence) or high (>5 % incidence) risk for mold infection.[85] While low-risk patients are "screened out" from intensive diagnostic monitoring or mold-directed antifungal prophylaxis, high-risk patients who develop fever undergo chest CT plus/minus pulmonary angiography within 72 hours. As outlined in their protocol, patients with a positive "occluded vessel" sign during CTPA or a "halo" sign when CTPA cannot be performed are initiated on systemic antifungal therapy, whereas those with nonspecific pulmonary infiltrates may receive a short course of empiric antifungal therapy and be considered later for antifungal de-escalation.[84] Data on the effectiveness and generalizability of this approach are certainly needed.

Review of drug-drug interactions (DDIs)

The drug expertise offered by an ASP can help manage the risk of DDIs that are of particular concern with antifungal drugs. An important example is management of the interaction between azole drugs and immunosuppressive agents in transplant patients. Azole drugs inhibit cytochrome P450 enzymes and/or the P-glycoprotein drug transporter and can alter the pharmacokinetic profile of other drugs including immunosuppressive agents, potentially leading to overdosing (with toxicity) or underdosing (with reduced efficacy) of both drugs.[86] An ASP team should include a clinical pharmacist with expertise in the pharmacokinetics of azoles and immunosuppressive drugs and their DDIs. Managing the DDI includes knowledge of the pharmacologic properties of azoles and immunosuppressive drugs in order to predict

Table 2. Studies comparing empiric versus preemptive antifungal therapeutic approach in high-risk neutropenic patients.

	Cordonnier et al. [81]	Morrissey et al. [82]	Hebart et al. [80]
Study design	Multicenter, randomized, open-label non-inferiority trial	Multicenter, randomized, open-label, parallel-group trial	Multicenter, randomized controlled trial
Study population	Adults with hematologic malignancies scheduled for chemotherapy or autologous transplantation	Adults with acute leukemia or who were undergoing allogeneic transplantation	Patients undergoing allogeneic transplantation
Number of patients	Empiric: 150 Preemptive: 143	Empiric: 122 Preemptive: 118	Empiric: 211 Preemptive: 198
Antifungal prophylaxis	Per institutional guidelines	Per institutional guidelines	Fluconazole 200 mg orally daily and/or amphotericin B suspension 4 × 5 mL/day
Screening strategy	Twice-weekly serum galactomannan until neutrophil recovery (all)	Twice-weekly serum galactomannan and polymerase chain reaction (inpatient) or once-weekly testing (outpatient) for 26 weeks or death (all)	Twice-weekly polymerase chain reaction for *Candida* and *Aspergillus* until day 30, then once- weekly testing after day 30 until day 90 (preemptive only)
Primary endpoint	No difference in survival (97.3% vs 95.1%, $P = 0.31$)	Significant reduction in empiric antifungal treatment in the preemptive arm (32% vs 15%, $P = 0.002$)	No difference in proven or probable invasive fungal infection (8.2% vs 8.2%)
Secondary endpoints	- More proven or probable invasive fungal infection in the preemptive arm (2.7% vs 9.1%, $P < 0.02$) - No difference in fever duration (median 13 vs 12 days, $P =$ not significant) - Increased mean duration of antifungal therapy in the empiric arm (7 vs 4.5 days, $P < 0.01$) - Higher mean cost of antifungals (2005€) in the empiric arm (2252 vs 1475, $P < 0.001$)	- No difference in all-cause mortality (15% vs 10%, $P = 0.31$) - More probable invasive aspergillosis in the preemptive arm (0% vs 14%, $P < 0.0001$) - No difference in hepatotoxic (17% vs 10%, $P = 0.11$) or nephrotoxic effects (43% vs 51%, $P = 0.2$)	- Higher mortality at day 30 in the empiric arm (6.3% vs 1.5%, $P = 0.015$) - No difference in survival at day 100 (16.4% vs 16.3%)

the potential clinical relevance of a potential DDI; appropriate monitoring of liver and/or renal tests; education to primary providers and patients; and TDM.[87,88] Various tools to assist ASPs in managing these DDIs are also available.[89]

Therapeutic drug monitoring

In many centers, it has become the standard of care to monitor serum voriconazole concentrations, and ASPs can incorporate TDM as part of antifungal stewardship efforts. This is particularly important for children, as there is very wide variability in the voriconazole dose required to achieve a target level between 1 and 5.5 mg/L. In one study, Spanish investigators followed 196 voriconazole trough levels in 30 children with IFI and found that 98 (50%) of the samples were reported as <1 mg/L and 14 (7%) were >5.5 mg/L.[90] The majority of patients (73%) required dose adjustment after the voriconazole trough was measured; a median voriconazole dose of 38 mg/kg/day for children < 5 y in contrast to a median dose of 15 mg/kg/day for children ≥5 y was also noted. The authors were unable to demonstrate a correlation between subtherapeutic level and poor outcome due to the small sample size. However, other studies have reported that voriconazole TDM improves the efficacy and safety for patients with invasive mycoses.[91-93] In a recent report, Park and colleagues randomized 110 adults with IFI into TDM or non-TDM groups.[92] Voriconazole dosage was adjusted to meet the target range of 1–5.5 mg/L based on the serum trough measured on the fourth day after initiation. Voriconazole TDM significantly reduced drug discontinuation due to adverse events (4% vs 17%, $P = 0.02$), and a higher proportion of patients achieved a complete or partial response with TDM (81%) compared to the non-TDM group (57%, $P = 0.04$).

While the evidence is more straightforward for voriconazole, the data supporting TDM for posaconazole require a nuanced interpretation. There are certainly studies that suggest a relationship between posaconazole concentrations and prophylactic efficacy, but it is not clear what target levels should be obtained and whether level results are a reliable indicator.[94-97] Although the effectiveness of posaconazole prophylaxis using the oral suspension was established without TDM in the 2 pivotal phase III prophylaxis studies[98,99], the proposed target concentration of 0.7 mg/L was derived from a post-hoc subgroup pharmacokinetic analysis from these 2 clinical trials.[95] However, this threshold remains a point of debate since the number of breakthrough IFIs was quite low.[100,101] In addition, Jang et al. noted that there were 3 patients who experienced breakthrough IFI even though their measured levels far exceeded the 0.7 mg/L

threshold, suggesting that prophylactic failure may not necessarily be contingent on level results.[95] It has been found that posaconazole penetrates alveolar cells and monocytes in concentrations that far exceed the blood, and this finding may be the explanation for why posaconazole is effective in preventing IFI despite low serum levels.[102] With regard to therapeutic efficacy, a target concentration of at least 1 mg/L has been proposed and is based on the study by Walsh et al. that showed improved clinical response rates with higher posaconazole levels in patients with established IFI on salvage therapy.[103] It is unknown how feasible it would be to attain and/or maintain such a level in practice.[100] Despite the issues that have been raised, posaconazole TDM has been advocated to identify patients who may benefit from correction of modifiable factors affecting oral bioavailability, dose adjustment, or switch to an alternative agent.[100] The availability of the delayed-release tablet may obviate the need for routine TDM, as serum posaconazole levels are achieved more reliably and without clinically relevant hepatotoxicity in comparison to the oral suspension.[104] There are no recommendations for monitoring serum concentrations of isavuconazole.

Thinking about metrics

Traditional ASPs use both *process* (i.e., those that measure the effect of an intervention on antimicrobial use) and *outcome* metrics (i.e., those that measure the effect of an intervention on resistance patterns and clinical outcomes) to assess the impact of AS interventions.[3] The updated 2016 IDSA and SHEA guideline for implementing ASPs suggests monitoring drug consumption via DOT.[2] However, DDD remains an alternative for healthcare systems that cannot obtain patient-level anti-infective usage data. While both DOTs and DDDs are standardized methods for measuring antimicrobial use, DOTs are not affected by dose adjustments, discrepancies between the DDD and preferred daily dose (such as would be seen in certain antifungal medications like amphotericin B deoxycholate, fluconazole, and itraconazole),[105] and can be used in both adult and pediatric populations, whereas DDDs have more limited use in pediatrics due to weight-based dosing.[106] Suggestions for both process and outcome metrics for antifungal stewardship are outlined in Table 3.[1] A recent US survey of adult and pediatric transplant centers found that monitoring is not done robustly in HCT or SOT patients despite the presence of an ASP with the exception of *Clostridium difficile* rates, followed by antimicrobial costs.[107] Because prescribing of antifungal agents is disproportionately high for transplant (and other highly immunocompromised) patients, efforts to examine whether antifungal stewardship interventions are effective in these patients should be encouraged. While standards have not been established regarding the frequency of monitoring, it seems reasonable to monitor an ASP's clinical impact at least annually with more frequent assessments depending on programmatic needs.

Table 3. Suggestions for process and outcome metrics for antifungal stewardship.

Process metrics	Examples of metric
Antifungal drug consumption	Days of therapy per 1000 patient-days OR Defined daily doses per 1000 patient-days
Compliance with institutional guidelines	
• Choice of drug	Proportion of patients treated with drug of choice for indication
• Dose	Proportion of patients prescribed appropriate dosing for indication
• Therapeutic drug monitoring	Proportion of patients on azole for whom serum level was checked appropriately from time of initiation
• De-escalation	Proportion of patients with fluconazole-sensitive *Candida* for whom therapy was switched from echinocandin (or other broad-spectrum agent) to fluconazole
• Intravenous-to-oral conversion	Proportion of patients taking an azole who were switched from intravenous to oral formulation
• Use of diagnostic tests	Proportion of high-risk patients in compliance with institutional recommendations for monitoring serum galactomannan
• Source control	Proportion of patients with candidemia with catheter removal
Outcome metrics	Examples of metric
Preventive strategies in high-risk patients	Episodes of invasive fungal infection in target groups
Treatment of invasive fungal infection	Proportion of patients with clinical cure Proportion of patients with candidemia with recurrent infection
Resistance	Proportion of *Candida* isolates caused by fluconazole-resistant strains
Cost	Total cost of prescriptions per year, stratified by antifungal drug

Evidence for antifungal stewardship

Several institutions have successfully implemented antifungal stewardship interventions using a multi-pronged approach that included post-prescription review and feedback, education, and the development of clinical guidelines.[108-110] One study reviewed 636 prescriptions, of which 72% were from the adult and pediatric hematology-oncology services, over 6 y.[108] The ASP provided feedback to the primary teams regarding diagnostic investigations, TDM, and antifungal prescribing and found a high compliance rate (88%) with ASP recommendations. Patient outcomes were favorable in 47 of 63 (75%) with IA and 52 of 60 (87%) with IC, and the total cost of antifungals was stable. A second study targeted high-cost antifungals in 173 patients at a tertiary hospital over a 12-month period.[109] The ASP provided clinical

advice during review of 45 (88.2%) micafungin, 70 (78.7%) voriconazole, 78 (62.4%) liposomal amphotericin B, and 3 (27.3%) caspofungin prescriptions. Except for voriconazole, nearly half of all treatments reviewed were stopped or changed, resulting in crude savings of ~£180,000 in antifungal drugs compared with the previous year. A similar program in Spain was also able to demonstrate a significant reduction in antifungal expenditures without increases in the incidence of IFI or 12-month mortality in patients with filamentous fungal infections.[110]

Studies specific to antifungal de-escalation have focused on candidemia with the advent of antifungal susceptibility testing. The timing of when to de-escalate has not been clearly established, but the 2016 IDSA guideline for the management of candidemia recommends transitioning from an echinocandin or amphotericin-based product to oral fluconazole (or voriconazole for *C. krusei* infection) within 5–7 d provided that the patient is clinically stable, has a susceptible isolate, and has negative repeat blood cultures on antifungal therapy.[111] In one report, Bal and colleagues devised an IV-to-oral policy that incorporated antifungal susceptibility testing of *Candida* blood isolates to guide antifungal de-escalation at their hospital and found significant cost-savings when 70.3% of patients with candidemia during the study period were able to be switched from an echinocandin or voriconazole to fluconazole.[112] In their retrospective study, Shah et al. evaluated the impact of antifungal susceptibility results in 103 patients receiving an echinocandin for candidemia; 89 were subsequently found to have fluconazole-sensitive isolates, but only 35 (39%) were switched to fluconazole.[113] While antifungal susceptibility testing was a potential tool, this study highlighted the importance of combining AS intervention(s) for optimal effect.

Although ASP interventions focusing on antifungal utilization can show benefit, these programmatic elements should be done in close collaboration with the primary teams (e.g., hematology-oncology, HCT, SOT, ICU). In addition, personnel staffing ASPs should develop expertise in diagnostics and TDM, in addition to prophylaxis and treatment of IFI, in order for antifungal stewardship efforts to be successful.

Conclusion

The current variability in antifungal use, inappropriate dosing, and delays in initiating appropriate therapy indicate a need for antifungal stewardship to improve the prevention, diagnosis, and management of IFI. While evidence from successful antifungal stewardship programs supports their benefits, additional questions regarding best strategies for implementation remain unanswered. As the availability of rapid molecular identification methods and non-culture-based diagnostics for IFI become more widely available, we need to better understand the optimal use of these tests, including in children, and the best ways to incorporate them into antifungal stewardship programs. In addition, it would be helpful to have guidance regarding appropriate de-escalation and duration of therapy for various IFI, as there is likely a link between exposure and development of antifungal resistance. Creating multi-institutional collaborative networks would be helpful to prospectively study these and other questions.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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